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MINI-REVIEW

Revisiting the gut-liver axis: gut lymphatic system in liver cirrhosis and portal hypertension

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Abstract

The lymphatic vascular system runs parallel to the blood vascular system, comprising a network of lymphatic vessels and secondary lymphoid organs. The intestinal lymphatic capillaries (lacteals) and the associated collecting vessels in the mesentery form the gut lymphatic system. The gut lymphatic vasculature comprises the longest-studied lymphatic vessel bed and plays a significant role in the uptake and transport of dietary fat, abdominal fluid balance, and gut immunosurveillance. Gut is closely connected to liver through the portal circulation. In several experimental and clinical studies, the "gut-liver-axis" has been demonstrated to contribute to the pathogenesis of portal hypertension, liver cirrhosis, and its complications. Given a significant impact of gut health on the liver, in the current review, we highlight "gut-liver axis" in context to the circulatory physiology of gut lymphatic vessels. Despite their paramount importance in maintaining fluid and immune homeostasis in the gut, gut lymphatic vessels remain one of the most understudied physiological systems in liver disease pathology. In the current review, we delineate the connections of gut lymphatics with abdominal fluid homeostasis and bacterial translocation in the pathogenesis of liver cirrhosis and portal hypertension. We describe mechanisms and factors that drive gut lymphangiogenesis and lymphatic vessel dysfunction during inflammation. The review also underscores the role of gut lymphatic endothelial cells in regulating gut and liver immunity. We finally discuss the prognostic and therapeutic prospects of studying gut lymphatic vessels in advanced liver cirrhosis.

ascites; cirrhosis; gut lymphatic vessels; immunity; portal hypertension

INTRODUCTION

Chronic liver diseases (CLDs) cause significant morbidity and mortality worldwide. CLDs can result due to multiple factors, including obesity, nonalcoholic fatty liver disease, alcohol abuse, hepatitis B or C infection, autoimmune diseases, cholestatic injury [caused by obstruction to bile flow, such as in primary (and secondary) biliary cholangitis, primary sclerosing cholangitis, and biliary atresia] and iron or copper overload that lead to chronic hepatic inflammation or cholestasis, and ultimately to liver fibrosis and cirrhosis (1). Cirrhosis is characterized by architectural changes in the liver such as fibrotic septa, vascular distortion, and regenerative nodules, resulting in resistance to portal blood flow in liver and elevated pressures in the portal venous system, termed portal hypertension (PHT) (2). Both cirrhosis and PHT either alone or in combination can cause multiple complications in patients, including ascites, varices, hepatic encephalopathy, coagulation defects, sepsis, hepatocellular carcinoma, etc. (1, 2).

The "gut-liver" axis contributes to CLDs, cirrhosis, and its complications in several ways, all leading to enhanced systemic inflammation via two routes (3). The first path carries bacterial and toxic products from the gut to the liver through portal circulation and then from the liver to the systemic circulation, and the second path transfers bacteria and other toxins directly from the gut via its lymphatic vascular system to the systemic blood via the thoracic duct. In homeostasis, gut lymphatic vessels play essential roles in the absorption and transportation of fat, maintaining tissue homeostasis and immunity, removing interstitial fluid and macromolecules, and returning them to the blood circulation, thereby preventing fluid accumulation and edema (3). Considering the close association of the gut with the liver, dysfunctional gut lymphatic vessels have been reported in experimental liver cirrhosis; however, how these vessels contribute to the pathogenesis and progression of liver cirrhosis remain largely unexplored (4). In the current review, we summarize the structure and function of gut lymphatic vessels and delineate their specific role and significance in liver cirrhosis.

GUT-LIVER AXIS IN LIVER CIRRHOSIS AND PORTAL HYPERTENSION

Depending on the etiology, CLDs may either involve degeneration and necrosis of hepatocytes or immune-mediated injury to the biliary epithelial cells/cholangiocytes, inflammation, liver sinusoidal endothelial cell dysfunction,

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distortion of the hepatic vascular architecture, and activation of myofibroblasts (1). Several cells, such as hepatic stellate cells, bone marrow-derived fibrocytes, portal fibroblasts, inflammatory cells, hepatocytes (via epithelial-mesenchymal transition), etc., have been identified as the source of activated myofibroblasts (5). Activated myofibroblasts result in the accumulation of the extracellular matrix and the development of fibrous septa and cirrhosis, reducing regular blood supply to the liver (6). These anatomical changes in the liver comprising micro- and macrovascular remodeling, neoangiogenesis, and nodule formation lead to increased vascular resistance and blood pressure within the portal vein, causing PHT (7). Besides changes in the liver, mesenteric splanchnic vasodilation and increased portal blood flow further aggravate PHT. Along with enhanced portal blood flow, other factors such as increased gut epithelial permeability, gut microbiota alterations, and impairment of local and general immune defense mechanisms have been reported to contribute to disease progression in human and experimental cirrhosis (8, 9). These changes cause increased pathological bacterial translocation from the gut leading to bloodstream infections, sepsis, multiorgan failure, and even death in patients with cirrhosis (9). The recent description of acute-on-chronic liver failure describes several precipitating factors from the gut that lead to acute deterioration of liver function, regardless of the underlying stage of cirrhosis (10).

GUT LYMPHATIC VESSELS

The lymphatic vessel network is a one-way open-ended drainage system involved in tissue fluid homeostasis and immune cell trafficking. The gut lymphatic vascular system comprises the intestinal lacteals, collecting lymphatic vessels, and lymph nodes, through which lymph flows and drains to the thoracic duct connecting the gut directly with the systemic circulation bypassing the liver (11). They are involved in fat absorption and transport, gut immunity, and homeostasis. Blind-ended lymphatic capillaries called lacteals are present in the intestinal villi, whereas collecting lymphatic vessels are present in the mesentery forming the largest lymphatic bed in the human body (Fig. 1). Absorption of the fluid occurs at the open-ended lacteals when interstitial fluid pressure is more than lumen pressure, forming lymph and drain into a submucosal lymphatic vascular network and then to mesenteric collecting lymphatic vessels. Before entering the systemic circulation, intestinal lymph is filtered of cell debris and pathogens by the draining lymph nodes.

Both lymphatic capillaries and collecting vessels are lined with lymphatic endothelial cells (LyECs). Capillary LyECs have open button-like junctions that form pores through which particulate matter, including large-sized particles (e.g., 150 nm diameter), and the interstitial fluid, can enter the vessel and form the lymph (12). In contrast, collecting LyECs have continuous "zipper-like" interendothelial tight junctions that prevent lymph leakage. These specialized zipper-like junctions between LyECs are similar to those present between blood vessel endothelial cells. Despite different functions, both button- and zipper-like junctions have a common protein assembly of anchoring and tight junction proteins. Anchoring junctions comprise VE-cadherin, β-catenin, and p-120 catenin, whereas tight junctions are composed of claudin-5, occludin, and zonula occludens (13). Specific loss of these junction components, primarily VE-cadherin, in LyECs causes lymphedema and inflammation (14). Along with zipper-like junctions, collecting lymphatic vessels like blood vessels also have smooth muscle cell layer and basement membrane. The intrinsic contractility of smooth muscle cells and arterial pulsations are necessary for lymph propulsion. The collecting lymphatic vessels also have bileaflet valves lined with both LyECs having zipper-like junctions and smooth muscle cells that prevent the backflow of lymph (15).

GUT LYMPHANGIOGENESIS

The formation of new lymphatic vessels from preexisting lymphatic vessels is termed as lymphangiogenesis. It is a dynamic process during mammalian embryogenesis but is largely absent in normal physiological conditions except in the meninges of the brain and intestinal lacteals. It usually occurs in pathology during inflammation, transplant rejection, and cancer metastasis (16).

During development, the lymphatic sac emerges by sprouting from the jugular veins when a distinct subpopulation of endothelial cells in these veins begin expressing Prox1 (17). Postnatal lymphangiogenesis involves sprouting, proliferation, migration, and tubule development of new lymphatic vessels from preexisting LyECs or from bone marrow-derived or circulating progenitor cells, capable of differentiating into LyECs, in the presence of prolymphangiogenic factors. During inflammation/disease, impairment of lymphatic function due to obstruction or obliteration of the lymphatic vessels causes stagnation of proteins and associated water in the interstitium, resulting in lymphedema (18). Under these conditions, lymphangiogenesis is triggered to compensate for impaired lymphatic drainage to maintain interstitial fluid homeostasis and clearance of inflammatory infiltrate and restore gut homeostasis. Lymphangiogenesis also enhances immune responses by promoting mobilization of immune cells such as macrophages and dendritic cells from the inflamed tissue to the draining lymph nodes (19).

Vascular endothelial growth factor-C (VEGF-C), a member of the VEGF growth factor family, is one of the key lymphangiogenic growth factors regulating the growth and maintenance of lymphatic vessels and is primarily produced by fibroblasts, macrophages, and LyECs as well. VEGF-C binds and autophosphorylates the homodimers of a tyrosine kinase receptor, vascular endothelial growth factor receptor 3 (VEGFR3) present on the LyECs, thereby activating the downstream proliferation signaling via Akt and/or ERK1/2 pathways (3). The neuropilin receptors, NRP1 and NRP2, act as coreceptors of VEGFR3. Apart from this, several other VEGF-C independent lymphangiogenic pathways directly activate the kinase activity of VEGFR3. For example, integrin β1-causes VEGFR3 activation upon mechanical stimulation of LyECs (20). FGF signaling also regulates the growth of lymphatic vessels via MYC expression.

Increased lymphangiogenesis is a prominent feature of gut inflammation. Studies have evaluated gut lymphatic vessels in intestinal bowel disease (IBD) and illustrated that there is significantly increased lymphangiogenesis along with lymphadenopathy, lymphangiectasia, and leakage that correlates with IBD severity. The morphological changes and

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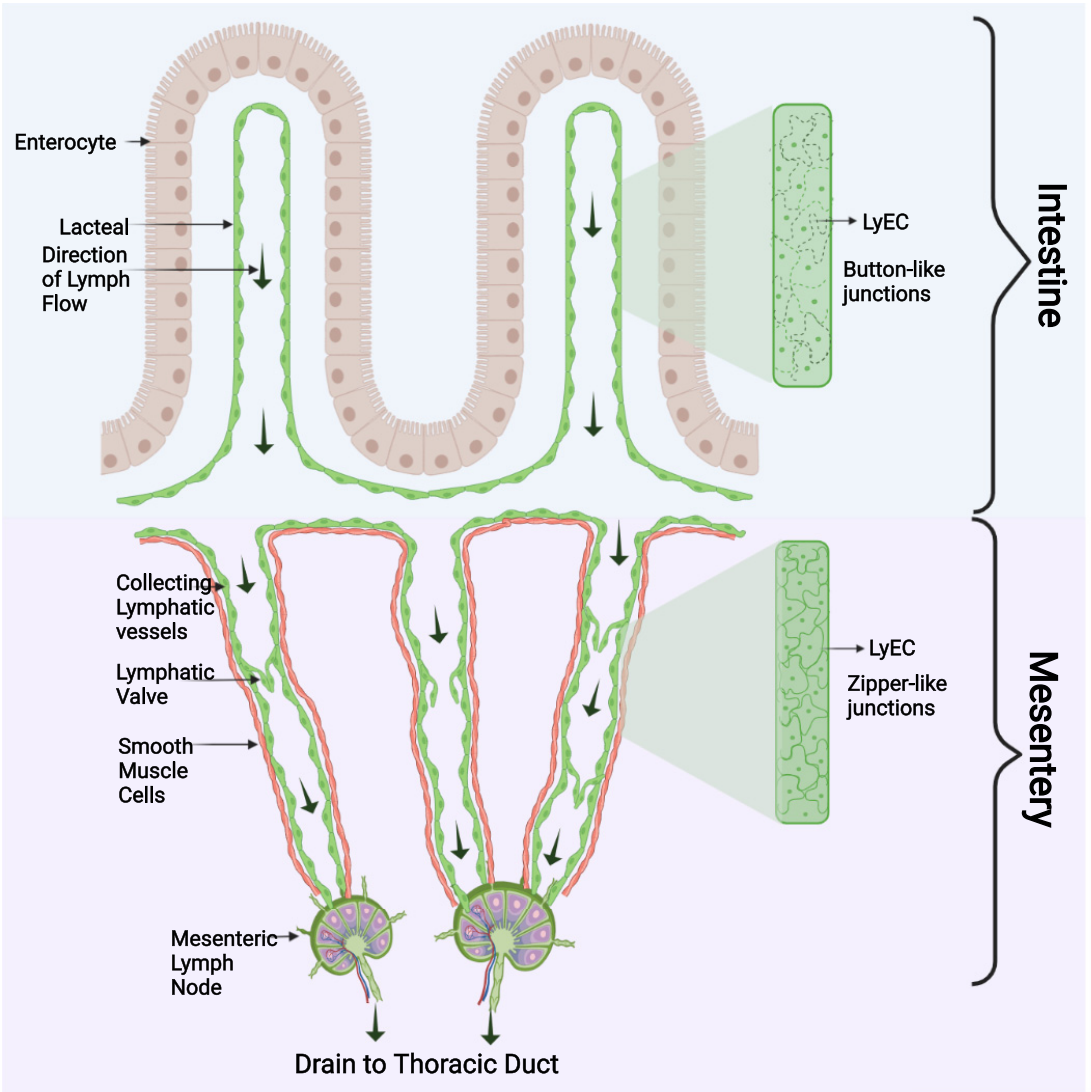

Figure 1. Anatomy of gut lymphatic system. Gut lymphatic system comprises lymphatic capillaries in the villi of small intestine with collecting lymphatic vessels and lymph nodes present in the mesentery. Both capillaries and collecting vessels are lined with lymphatic endothelial cells (LyECs). Presence of loose button-like junction between LyEC of lymphatic capillaries make them permeable to large size molecules. They absorb nutrients, fats, immune cells, and interstitial fluid and form lymph which flows down to collecting lymphatic vessels. Zipper-like junctions between LyECs of collecting lymphatic vessels prevent lymph leakage. Lymphatic valve between collecting lymphatic vessels allow one-way flow of lymph. Smooth muscle cells covering the collecting lymphatic vessels and valves allow the propulsion of lymph to nodes for immunosurveillance. After filtering through the nodes, lymph reaches the thoracic duct which ultimately drains into the left subclavian vein.

remodeling of the lymphatic vessels have been demonstrated in the lacteal lymphatic capillaries, the collecting mesenteric lymphatics, and also the mesenteric lymph nodes (MLNs) (21). Similar to IBD, obesity is also associated with increased gut lymphangiogenesis, dysfunction, and leakage (22).

Along with lymphangiogenesis, another feature of intestinal (particularly mesenteric) lymphatics in gut inflammation is the altered contractile activity and dilation of lymphatic vessels, where inflammatory mediators are known to negatively regulate lymphatic contractions (23).

Unlike gut inflammatory disorders, not many studies have reported the remodeling of gut lymphatic vessels in CLD and cirrhosis. In a study, it has been reported that lymphatic vessels exhibit decreased lymphatic drainage due to increased endothelial nitric oxide synthase (eNOS) in inflamed lymphatic endothelium in experimental models of liver cirrhosis (4). A dysfunction of the liver lymphatic system has also been reported in CLD, irrespective of the etiology (24). Mounting evidence shows that after gut injury or infection, intestinal lymphatics serve as the primary route for nonbacterial gut-derived factors, inducing systemic inflammation, respiratory failure, and organ dysfunction (25). Thus, modulation of the gut lymphatics, VEGF-C-VEGFR3 signaling pathway, and lymphangiogenesis may serve as a potential therapeutic strategy to resolve inflammation in liver cirrhosis and its complications. Studies in rat models of sepsis have indicated that ligation of the mesenteric lymphatic vessel or induction of its drainage by a polyethylene catheter inserted into mesenteric lymphatic vessel lead to a

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significant amelioration of inflammatory lung injury, decreased neutrophil activation, and inhibition of endothelial apoptosis to preserve the pulmonary barrier function (26). Therapy with lymphangiogenic growth factors such as VEGF-C that promotes the growth and functions of the lymphatic vessels to facilitate fluid flow, drainage, bacterial antigen, and inflammatory cell clearance has also emerged as a potential therapeutic strategy for IBD and other chronic inflammatory diseases (27). Well-planned and comprehensive studies are required to understand how gut lymphatic vessel modulation and therapeutic lymphangiogenesis using VEGF-C would impact the progression of liver cirrhosis.

CONTRIBUTION OF GUT LYMPHATIC SYSTEM TO THE FORMATION AND ACCUMULATION OF ASCITES

One of the mechanisms of ascites formation in cirrhosis is the excessive formation of interstitial edema that exceeds the capacity of the gut and liver lymphatic system for draining splanchnic and hepatic lymph back to the blood circulation (28). The interstitial fluid gets accumulated into the peritoneal cavity and forms ascites. The hypothesis of lymph imbalance linking the gut lymphatic system to the accumulation of ascites was proposed in 1980. They suggested that during the formation of ascites, the volume of splanchnic lymph produced far exceeds the volume of lymph returned into the blood circulation (29). This imbalance is responsible for an altered distribution of the extracellular fluids that stimulates renal retention of salt and water and, consequently, the accumulation of fluid in peritoneal space, causing ascites. Compared with the lymphatic flow in healthy subjects (1 L/day), studies have demonstrated a significant increase in both the abdominal lymph production (30-fold) and lymph flow in the thoracic duct of patients with cirrhosis (8–9 L/day) (30). Increased PHT is the most obvious cause of fluid leakage from the lymphatic vessels in the abdominal cavity. Lymph production and flow in the gut correlate positively with increasing portal pressures. In health, the gut lymphatic vessels drain a moderate amount of lymph and return it back to systemic circulation, preventing accumulation of fluid in the abdominal cavity. But because of increased portal pressures and back flow of blood from liver to gut, the gut lymphatic system is unable to compensate the overwhelmed lymph production, thus resulting in ascites formation in the peritoneal cavity.

Studies examining the role of gut lymphatic abnormalities in decompensated cirrhosis and ascites are meagre. Ribera et al. have documented that a chronic eNOS inhibition in mesenteric lymphatic vessels improves lymphatic drainage, reducing ascites (4). In our ongoing studies, we have also observed a beneficial role of VEGF-C in experimental models of liver cirrhosis in terms of improved lymphatic drainage and clearance of ascites (31).

BACTERIAL TRANSLOCATION IN LIVER CIRRHOSIS AND GUT LYMPHATICS

The trafficking of bacteria, their products, and immune cells to the MLNs via gut lymphatic vessels is an integral part of the gut immunity in homeostasis. The gut-associated lymphoid tissue including Peyer's patches and MLNs confine the commensal bacteria to the gut, preventing their unwanted systemic exposure and subsequent immune responses. The relevance of gut lymphatics in containing bacterial infection has been revealed in a study where ablation of intestinal and MLN lymphatics using transgenic mice models resulted in 100% mortality within 60 h due to sepsis (32).

During CLD, increased gut permeability and bacterial load along with dysfunctional gut immune responses cause an ineffective elimination of the bacteria in the MLNs. This aggravates bacterial trafficking to the blood, enhancing systemic immune responses and thus contributing to the progression of cirrhosis and associated complications (33). The portal vein has been considered as the primary draining system for endotoxins present in the bowel or the peritoneal cavity. However, upon portal vein occlusion in rats, endotoxins still enter the systemic circulation (34). These results are indicative of an alternative route of transport for intestinal endotoxins. Indeed, a substantial proportion of radiolabeled endotoxins injected in the peritoneal cavity in dogs have been recovered from the thoracic duct. Comparative and kinetic studies assessing the lymphatic and portal venous route with respect to bacterial translocation in liver cirrhosis are lacking and are needed to dissect the relative contributions of these two systems toward systemic inflammation in cirrhosis.

An acute bacterial infection of the abdominal fluid or ascites in the absence of any intra-abdominal, surgically treatable source of infection is termed spontaneous bacterial peritonitis (SBP) (35). The presence of SBP suggests the failure of lymphatic channels in the gut. Positive bacterial cultures of the MLNs and altered intestinal permeability as assessed by ^{51}Chromium-labeled-ethylenediaminetetraacetic acid permeability test are mostly seen in Child–Pugh C cirrhotic and those with ascites as compared with Child A cirrhotic (36). In experimental studies, it has been demonstrated that green fluorescent protein (GFP)-labeled *Escherichia coli* administered orally to cirrhotic rats can be seen in the intestinal lumen, MLN, and ascites (37). Hence, it may be deduced that defective gut lymphatic vessels and immunosurveillance in the gut and MLNs that fail to effectively transport and/or eliminate bacteria and their products might be one of the key reasons of SBP followed by systemic infections and inflammation leading to sepsis in patients with cirrhosis.

LyECs IN THE MESENTERIC LYMPH NODES AND GUT IMMUNITY

Several studies have reported the direct interactions of LyECs with several immune cells (Fig. 2). These interactions are made possible through the precise anatomical location of LyECs, chemokine gradients, and expression of antigen-presenting and adhesion molecules by LyECs (38). During homeostasis, LyECs in MLNs exhibit a tolerogenic phenotype to maintain peripheral tolerance to self-antigens in the lymph. They maintain peripheral T-cell fate and function via the expression and presentation of endogenous oral

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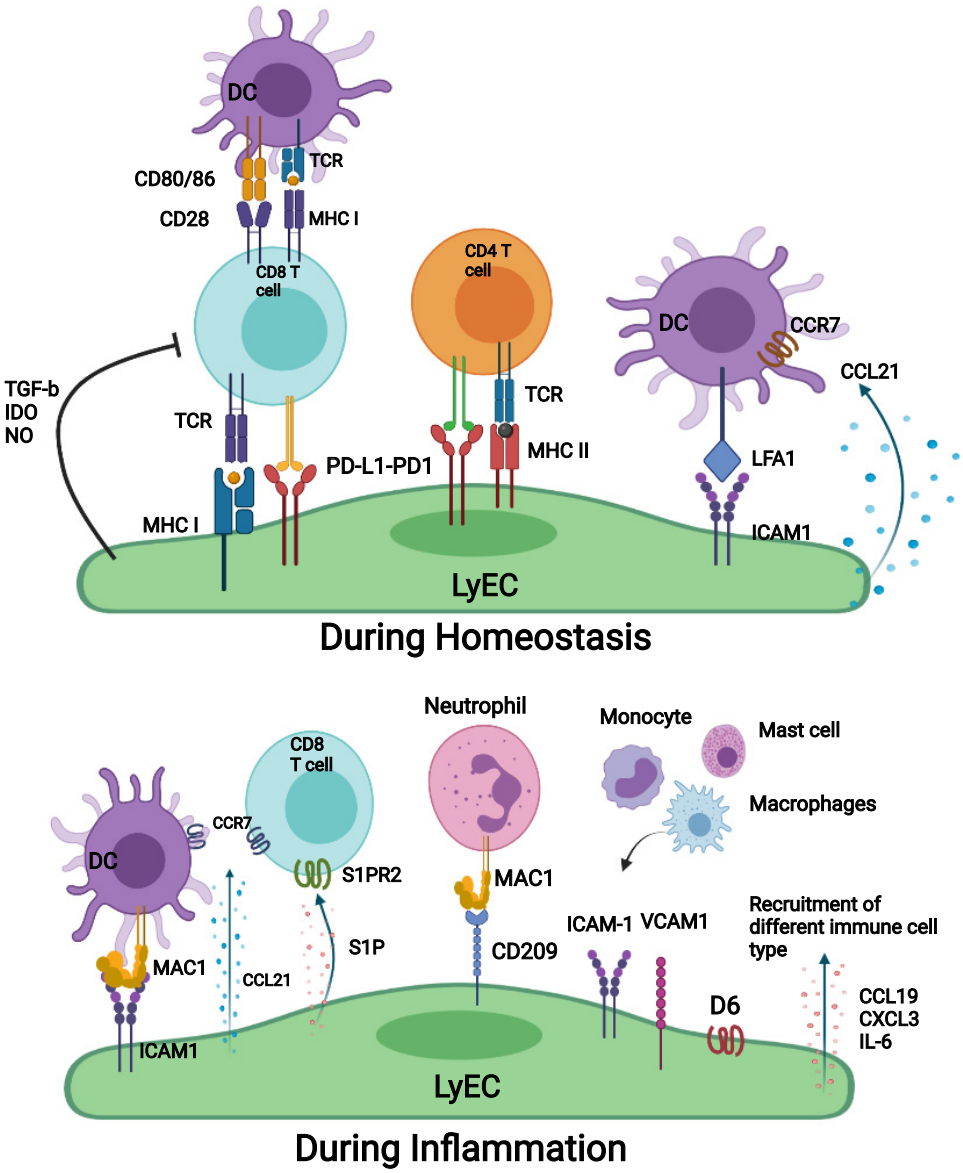

Figure 2. Interactions of lymphatic endothelial cells (LyECs) with immune cells under homeostasis and inflammatory conditions. During homeostasis, LyECs in the mesentery and the mesenteric lymph nodes (MLNs) secrete various immunoregulatory factors, such as, TGF-β, indoleamine-2,3-dioxygenase, and nitric oxide. They interact with T cells and DCs by various inhibitory receptors and prevent their proliferation and activation. LyECs act as antigen-presenting cells by expressing MHC I and II molecules, and present antigens to T cells. Inflamed LyEC, however, overexpress chemokines including CCL21, CCL19, IL-6, CXCL13, and S1P that traffic immune cells to nearby lymph nodes for adaptive immune response. Inflamed LyECs increases the expression of adhesion molecules such as CD209, ICAM-1, and VCAM-1 which helps in the adhesion of immune cells. CCL, chemokine (C-C motif) ligand; CCR7, chemokine receptor 7; CXCL13, chemokine (C-X-C motif) ligand 13; DCs, dendritic cells; ICAM-1, intercellular adhesion molecule 1; IDO, indoleamine-2,3-dioxygenase; IL-6, interleukin 6; LFA1, lymphocyte function-associated antigen 1; MAC1, macrophage-1 antigen; MHC, major histocompatibility complex; NO, nitric oxide; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; S1P, Sphingosine-1-phosphate; TCR, T-cell receptor; TGF-β, transforming growth factor β; VCAM1, vascular cell adhesion protein 1.

antigens and tissue-specific antigens. LyECs express major histocompatibility complex (MHC) class I and class II molecules and can directly induce T-cell tolerance via clonal deletion of self-reactive CD8 T cell, expansion of regulatory T cells, and suppression of dendritic cell (DC)-mediated T-cell activation (39). They can directly dampen DC maturation as well (40). A variety of immunoregulatory factors are expressed and secreted by LyECs such as, TGF-β, indoleamine-2,3-dioxygenase, and nitric oxide, all of which are immunosuppressive in nature (41). LyECs also express high levels of the inhibitory receptor PD-L1 and suboptimal levels of costimulatory molecules such as CD80 and CD86, suggesting that healthy LyECs act as tolerogenic antigen-presenting cells (42).

Inflamed LyECs, however, change their phenotype to immunogenic by increasing the expression of adhesion molecules and chemokines to facilitate activated immune cell trafficking to nearby draining MLNs to generate adaptive immune responses. Activated DCs with high expression of CCR7, migrate to MLNs in response to CCL21 and CCL19 secreted by the LyECs (43). DCs present antigen to $CD4^+$ T cells, or cross-present to $CD8^+$ T cells, thereby regulating the adaptive immune response. To keep the inflammation in check, LyECs start expressing D6 receptor that helps in scavenging proinflammatory chemokines while sparing homeostatic chemokines (42). D6 receptor also helps the LyECs to discriminate between mature and immature dendritic cells (44). During inflammation, LyECs further secrete a lipid mediator, Sphingosine-1-phosphate (S1P) that binds to S1P receptor on T cells and aids in their migration to the MLNs (45). Apart from DC and T cells, LyECs are known to attract other immune cells such as neutrophils and macrophages in MLNs (42). Direct interactions of LyECs with lymphocytes also affect their proliferation and activation in inflammatory conditions (38). LyECs, particularly those lining the MLNs are thus capable of directly shaping the immune response through influencing immune cell trafficking, activation, proliferation, and antigen

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presentation during inflammation. The phenotype and functions of mesenteric LyECs and their interactions with other immune cells during different stages of liver cirrhosis remain elusive and thus warrants further investigations.

CONCLUSIONS

Gut lymphatics represents a new and yet unexplored frontier in liver cirrhosis. Given the importance of the gut-liver axis in several pathogenesis mechanisms of cirrhosis and its complications, it is highly pertinent to explore and image these vessels in cirrhosis in both preclinical and clinical studies. In preclinical models of toxin-induced cirrhosis, functional lymphatic vessels have been visualized by intravital microscopy using tracer dyes, such as Evans blue or fluorescent dextran (4). Besides this, noninvasive protocols using genetic reporter mice such as green fluorescent protein (GFP)-vegfr3 or GFP-Prox1 mice are now available (46). These reporter mice could be developed into models of cirrhosis of varying severity stages (toxin or diet-induced) and thus provide valuable information on lymphatic remodeling in the progression of the disease. In humans, lymphatics are being imaged by several modalities that allow for qualitative and quantitative assessment of the lymphatic system, pre-or intraoperatively in surgical procedures where lymphatics are involved (47). Although, currently, there are no guidelines for imaging gut lymphatic vessels for diagnosis or prognosis of cirrhosis in a clinical scenario, investigational studies with high resolution and deep imaging techniques would provide insights on how lymphatic abnormalities correlate with the disease severity and outcome in patients with cirrhosis. Dissecting changes in the gut lymphatic vessels and LyECs using advanced imaging and single-cell sequencing technologies would shed light on how they impact bacterial translocation, ascites formation, gut, and systemic immune responses in advanced liver diseases, thus leading to novel therapeutic strategies.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.K. conceived and designed research; P.J. and D.M.T. prepared figures; P.J. drafted manuscript; P.J., D.M.T., and S.K. edited and revised manuscript; D.M.T. and S.K. approved final version of manuscript.

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